Pharmacy Policy

Urea Cycle Disorder Agents

Policy Number: 9.038
Version Number: 5.0
Version Effective Date: 07/06/2016

Product Applicability

☐ All Plan* Products

Well Sense Health Plan
- New Hampshire Medicaid
- NH Health Protection Program

Boston Medical Center HealthNet Plan
- MassHealth
- Qualified Health Plans/ConnectorCare/Employer Choice Direct
- Senior Care Options

Note: Disclaimer and audit information is located at the end of this document.

Policy Summary

The Plan will authorize coverage of urea cycle disorder agents when appropriate criteria are met.

Description of Item or Service

The urea cycle is the metabolic pathway that transforms nitrogen to urea for excretion from the body. When there is a deficiency of an enzyme in this pathway, a patient can develop a urea cycle disorder (UCD). UCDs are:

- Carbamoyl phosphate synthetase I (CPSI) deficiency
- Ornithine transcarbamylase (OTC) deficiency
- Argininosuccinate synthetase (ASS) deficiency
- Argininosuccinate lyase (ASL) deficiency
- N-acetyl glutamate synthetase (NAGS) deficiency
- Arginase deficiency

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Except for arginase deficiency, UCDs result in hyperammonemia and are life-threatening. The initial approach to treatment consists of rehydration and maintaining good urine output, removing nitrogen from the body via medications and/or hemodialysis, stopping protein intake, minimizing catabolism, and stimulating anabolism and uptake of nitrogen precursors by muscle.

N-acetyl glutamate synthetase (NAGS) is one of many enzymes involved in the pathway, and its deficiency can cause a urea cycle disorder that results in hyperammonemia and life-threatening illnesses. Survivors of the metabolic decompensation frequently have severe neurologic injury that correlates with the cumulative duration of hyperammonemia. Prompt recognition and treatment are needed to improve outcome. Hemodialysis is the quickest and most efficient method and should be used if ammonia is rapidly increasing, if the acute hyperammonemia is resistant to initial drug therapy, and/or the ammonia is persistently above the range of 350 to 400 micromol/L.

Carglumic acid (Carbaglu®) is the only product FDA-approved as a specific treatment of hyperammonemia due to NAGS deficiency. Carglumic acid activates the first enzyme of the urea cycle (CPSI), leading to rapid reduction of plasma ammonia to normal levels. It is approved for use in acute and chronic hyperammonemia due to NAGS deficiency. Sodium phenylacetate-sodium benzoate may also be used in addition to carglumic acid if the hyperammonemia is severe; otherwise carglumic acid can be used alone.

Carglumic acid was shown to effectively and rapidly reduce plasma ammonia levels within 24 hours of initiation of treatment and normalize ammonia levels within 3 days of initiation of treatment in patients with NAGS deficiency in a retrospective case series review. Additionally, patients with NAGS deficiency treated chronically with carglumic acid maintained normal plasma ammonia levels for the duration of treatment. The initial dose for acute hyperammonemia ranges from 100 to 250 mg/kg/day orally (prepared as a liquid and divided into two to four doses that are given immediately before meals). The dose is adjusted according to the patient’s symptoms and plasma ammonia level. The dose for maintenance treatment of chronic hyperammonemia is typically <100 mg/kg/day. The adverse reactions to carglumic acid include vomiting, abdominal pain, fever, tonsillitis, anemia, ear infection, diarrhea, nasopharyngitis and headache.

Ravicti® (glycerol phenylbutyrate) is approved for use as a nitrogen-binding agent for chronic management of adult and pediatric patients 2 years of age and older with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti® should be used in conjunction with dietary protein restriction and, in some cases, dietary supplements (essential amino acids, arginine, citrulline, and protein-free calorie supplements). Patients should take Ravicti® with food and administer directly into the mouth via oral syringe or dosing cup. Dosing is based on body surface area; the maximum daily dose is 17.5 mL (19 grams).

Ravicti® was evaluated in four clinical trials; two evaluated treatment in adults, while the other two evaluated Ravicti® in children 2 to 17 years of age. The first study evaluating Ravicti® in adults was a randomized, double-blind, active-controlled, noninferiority trial that compared Ravicti® with sodium phenylbutyrate (Buphenyl®) in patients with UCDs who had been on sodium phenylbutyrate prior to enrollment. Patients were required to have a deficiency involving CPS, OTC, or ASS. Ravicti® was noninferior to sodium phenylbutyrate with regards to the 24-hour AUC for ammonia. Another long-term, twelve month uncontrolled, open-label study evaluated monthly ammonia control and hyperammonemic crisis over twelve months in adults. Patients were converted

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from sodium phenylbutyrate to Ravicti®. During the study period, mean fasting venous ammonia values were within normal limits; seven patients reported ten hyperammonemic crises overall.

The efficacy of Ravicti® in pediatric patients was evaluated in a seven-day study and a ten-day study. Sodium phenylbutyrate or Ravicti® was administered in divided doses to patients with UCD subtypes OTC, ASL, and ASS. The 24-hour AUCs for blood ammonia were similar between the treatment arms.

Ravicti® should not be used for the treatment of acute hyperammonemia in patients with UCDs, nor should it be used for the treatment of NAGS deficiency because safety and efficacy have not been established. Use of Ravicti® is contraindicated in patients less than 2 months of age due to immature pancreatic exocrine function, leading to insufficient drug metabolism.

Policy

The Plan may authorize coverage of Carbaglu® and Ravicti® for members meeting the following criteria:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Approval Criteria</th>
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| **Carbaglu®** | Documentation of the following:  
1. A diagnosis of hyperammonemia due to the deficiency of the hepatic enzyme N-acetylglutamate synthase confirmed by enzyme analysis or DNA mutation analysis (plasma ammonia level within past 3 months must be included); **OR**  
2. A diagnosis of hyperammonemia (plasma ammonia level within past 3 months must be included) due to suspected deficiency of the hepatic enzyme N-acetylglutamate synthase. **(approval duration: 3 months)** |
| **Ravicti®** | Documentation of the following:  
1. Age 2 years or older; **AND**  
2. A diagnosis of a urea cycle disorder (UCD) **(except NAGS); AND**  
3. Failure to manage UCD with dietary protein restriction and/or amino acid supplementation alone; **AND**  
4. Inadequate response, intolerance, or contraindication to sodium phenylbutyrate (Buphenyl®); **AND**  
5. Ravicti® is being used as an adjunct to at least one of the following therapies:  
   a. Dietary protein restriction; **OR**  
   b. Dietary supplements (e.g., arginine, citrulline, essential amino acids, protein-free calorie supplements) |
Medication | Approval Criteria
---|---
**Re-Authorization**

### Carbaglu®
- Documentation of the following:
  1. Clinical response to Carbaglu® treatment (a normal or improved ammonia level within the past 6 months must be included); **OR**
  2. Enzyme analysis or DNA mutation analysis confirming N-Acetylglutamate synthase deficiency if a 3 month trial was approved previously.

### Ravicti®
- Documentation of the following:
  1. Clinical response to Ravicti® treatment; **AND**
  2. Member is actively on protein-restricted diet or is taking Ravicti® in conjunction with dietary supplements (e.g., arginine, citrulline, essential amino acid, protein-free calorie supplements).

### Limitations
The Plan will **not** approve coverage of Carbaglu® or Ravicti® in the following instances:
- When the above criteria are not met.
- Use of Ravicti® in a member less than 2 months old.
- Use of Ravicti® for diagnosis of N-acetylglutamate synthase (NAGS) deficiency
- Use of Ravicti® for treatment of acute hyperammonemia.

### Clinical Background Information and References

### Appendix A – Quantity Limitations

<table>
<thead>
<tr>
<th>Medication Name and Strength</th>
<th>Maximum Quantity</th>
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<tbody>
<tr>
<td>Ravicti® 1.1 grams/mL</td>
<td>525 mL per 30 days</td>
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### Original Approval Date

<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date</th>
<th>Policy Owner</th>
<th>Approved by</th>
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Policy Revisions History

<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date</th>
<th>Approved by</th>
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<tbody>
<tr>
<td>12/01/2013</td>
<td>Policy applied to NH Medicaid</td>
<td>12/01/2013</td>
<td>P&amp;T Committee</td>
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<td>NH DHHS</td>
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<tr>
<td>12/13/2013</td>
<td>Policy applied to ConnectorCare/Qualified Health Plan (QHP)</td>
<td>04/01/2014</td>
<td>P&amp;T Committee</td>
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<tr>
<td>3/13/2014</td>
<td>P&amp;T annual review, no changes were required.</td>
<td>07/01/2014</td>
<td>P&amp;T Committee</td>
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<tr>
<td>03/12/2015</td>
<td>P&amp;T annual review, changed title of policy from “Carbaglu®” to “Urea Cycle Disorder Agents”, added criteria and quantity limit for Ravicti® to policy</td>
<td>07/01/2015</td>
<td>P&amp;T Committee</td>
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<td>NH DHHS</td>
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<tr>
<td>03/10/2016</td>
<td>P&amp;T annual review, no criteria changes</td>
<td>07/06/2016</td>
<td>P&amp;T Committee</td>
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Next Review Date

03/09/2017

Other Applicable Policies

9.002 Mandatory Generic Substitution Policy
9.015 Quantity Limitation Policy

Reference to Applicable Laws and Regulations, If Any

Disclaimer Information

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

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Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.

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